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# Dicentric Isochromosome for the Long Arm of Chromosome #17, dic i(17q), in a Patient with Chronic Myelogenous Leukemia (CML)

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**ABSTRACT:** Cytogenetic studies in a 33-year-old male patient with chronic myelogenous leukemia of 7 years duration revealed a so-called i(17q) chromosome marker and other cytogenetic abnormalities during the early phase of blastic crisis which were not present at diagnosis. Careful morphologic examination of this marker using G- and C-banding techniques revealed it to be a dicentric chromosome with a very short intercentromeric area. The fact that the dicentric nature of this marker was not apparent with the conventional Giemsa stain emphasizes the usefulness of the C-banding technique in defining the origin of this important cytogenetic marker.

An isochromosome of the long arm of chromosome #17, i(17q), has been observed in myelo- and lymphoproliferative disorders, in reticuloendothelial neoplasia [1-9], and in the bone marrow of a patient with metastatic cancer of the prostate as well [10]. The role of this marker in the course of blastic transformation of chronic myelogenous leukemia (CML) has been emphasized by many authors [11-17] and identification of clones bearing this isochromosome has invariably predicted the accelerated phase of blastic crisis preceding observable hematologic change.

Prior to the development of the banding techniques, the i(17q) was described as an abnormal metacentric chromosome, intermediate in size between the C and E group chromosomes. G- (Giemsa) and Q- (fluorescence) banding studies later proved it to be an isochromosome formed by misdivision of the centromere.

In this report, we present the cytogenetic and hematologic data from a case of CML of seven years duration in which this marker chromosome and other cytogenetic abnormalities, not present at diagnosis, were observed during the early phase of blastic crisis. We also present a closer look at the morphology of this marker as revealed by G and C (constitutive heterochromatin) banding.

## CASE REPORT

This 33-year-old male was first seen at the District of Columbia General Hospital on December 22, 1970 for narcotic withdrawal. A routine blood count showed a WBC of 105,000/mm<sup>3</sup> with a differential of 47% polymorphonuclear neutrophils, 12% bands, 16% metamyelocytes, 15% myelocytes, 1% myeloblasts, 7% lymphocytes, and 2% basophils; leukocyte alkaline phosphatase was markedly decreased and platelets

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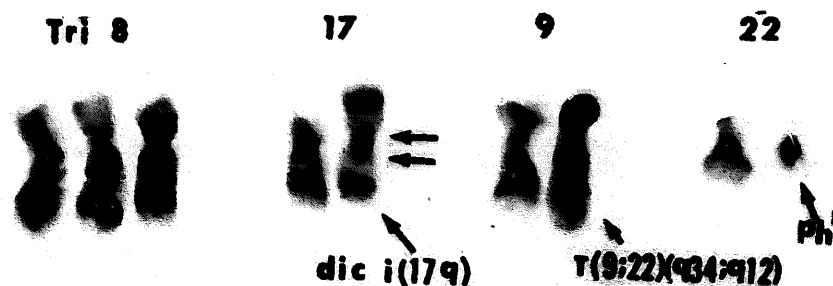
appeared normal on the blood smear. Physical examination revealed a spleen enlarged to 4 cm below the midclavicular line and a liver palpable to 6 cm below the right costal margin. A diagnosis of CML was made but no treatment was given at this time. The patient was temporarily lost to follow-up but returned to the clinic on March 16, 1971 complaining of weakness, fatigue, and a weight loss of 20 pounds. Repeat peripheral blood studies revealed a WBC of  $120,000/\text{mm}^3$  with 36% polymorphonuclear neutrophils, 34% bands and metamyelocytes, 15% myelocytes, 11% promyelocytes, 2% myeloblasts, 1% basophils, and 1% lymphocytes; hematocrit 35.5%, hemoglobin 12.6 g%, and platelets  $214,000/\text{mm}^3$ . A bone marrow aspirate obtained on March 19, 1971 was hypercellular with an E:M ratio of 1:10 and no increase in blasts. Cytogenetic studies were also obtained on this specimen.

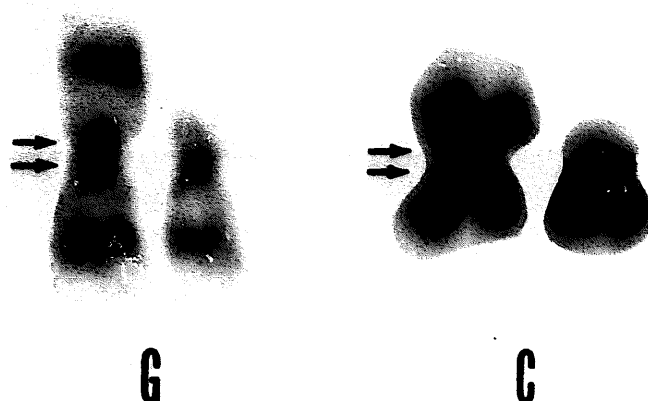
Treatment with  $^{32}\text{P}$  was begun March 22, 1971 at an initial dose of 5 mCi; between March 1971 and September 1972 the patient received a total of 24.8 mCi  $^{32}\text{P}$ , which kept his disease under reasonable control. Intermittent myleran therapy was administered from January 1973 to August 1977 with excellent response until December 1977 when leukocytosis of  $16,000/\text{mm}^3$  and an increase in the number of blasts (8%) were noted in the peripheral blood. Cytogenetic studies were attempted on both the bone marrow and peripheral blood on January 4, 1978. The bone marrow aspirate was unsuccessful and a biopsy showed a hypercellular marrow with predominance of immature myeloid cells. By January 6, 1978, the WBC had increased to  $47,300/\text{mm}^3$  with 55% blasts. He was treated with vincristine and prednisone, and splenic irradiation (700 rads) for relief of extreme pain due to massive splenomegaly (22 cm). The WBC, however, continued to rise ( $70,000/\text{mm}^3$  with 90–95% blasts). Hydroxyurea treatment, 500 mg twice daily, was instituted, decreasing the WBC to  $33,000/\text{mm}^3$ , but the patient's condition continued to deteriorate with the development of fever, and pleural and pericardial effusions. He died on February 8, 1978; no autopsy was performed.

## CYTOGENETIC RESULTS

All the metaphases analyzed from the bone marrow specimen of March 19, 1971 had a karyotype of 46,XY,Ph<sup>1</sup>. Repeat chromosome studies on the bone marrow of January 4, 1978 were not successful; a peripheral blood specimen obtained the same day was cultured for 1 and 2 days. In the 1-day unstimulated culture, all 40 analyzed metaphases had one Philadelphia chromosome (Ph<sup>1</sup>): 10% of the cells had 44 to 45 chromosomes (this hypodiploidy was presumed to be artifactual, since the missing chromosome varied from cell to cell); 75% of the cells had 47 chromosomes, including an extra #8 chromosome, the typical Ph<sup>1</sup> translocation, and a so-called i(17q) (Fig. 1). The remaining 15% of the cells had 46 chromosomes: 1 cell had a 46,XY,t(9;22) (q34;

**Figure 1** Partial G-banded karyotype of a cell from a 1-day unstimulated peripheral blood culture showing an extra #8 chromosome, t(9;22), and dic i(17q).





**Figure 2** Enlarged dic i(17q) and the normal homologous #17 (G and C banding).

q12) karyotype while the other 5 cells appeared to be of the same clone as the cells with 47 chromosomes, since they all had the i(17q) marker and an extra #8 but were missing a chromosome, which varied from cell to cell. In the 2-day phytohemagglutinin-stimulated culture, 10% of the cells had a normal male karyotype, 46,XY, and 90% were Ph<sup>1</sup> positive; of the latter group, 7% had 46 chromosomes, 16% had 48 chromosomes (no detailed analysis was possible in these cells), and 67% had 47 chromosomes with the same karyotype as described above.

The morphology of the so-called i(17q) marker is shown in Figures 1 and 2. Figure 1, a partial G-banded karyotype demonstrates t(9;22), an extra #8, and the marker chromosome i(17q). This marker, which was originally thought to be an isochromosome, i(17q), appears on closer examination to be a dicentric chromosome with a very short intercentromeric area. The dicentric nature of this marker is not apparent with the conventional Giemsa stain where it looks like a metacentric chromosome, but it is demonstrable with both G banding and, especially, C-banding. An enlargement of the marker, shown with the normal homologous #17 in Figure 2, clearly shows two centromeres, with the break point in the p11 location. We have designated this marker dic i(17q). This finding is in agreement with cytogenetic results in two cases published by McDermott et al. [18] where the dicentric i(17q) appeared in both patients at the time of acute myeloblastic transformation; in addition, one showed trisomy #8.

In many of the papers which report the i(17q) chromosome, the authors have employed either G or Q banding, but very few have reported results with C banding. If this were done, it is possible that some, if not all, of these so-called isochromosomes would demonstrate two centromeres. More frequent usage of C banding in such situations could possibly elucidate the origin of this important cytogenetic marker.

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